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Customer No.: 07278
PATENT TRADEMARK OFFICE

Docket No.: 5432/0J951US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Connie SANCHEZ and Sandra HOGG

Serial No.: 10/021,126 Art Unit: 1614

Confirmation No.: 7268

Filed: December 12, 2001 Examiner: Frederick F. KRASS

For: TREATMENT OF NEUROTIC DISORDERS

CLAIM FOR PRIORITY

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

Applicant hereby claims priority under 35 U.S.C. Section 119 based on Denmark application No. PA 1999 00991 filed July 8, 1999.

A certified copy of the priority document is submitted herewith.

Respectfully submitted,

Dated: February 21, 2003

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Kongeriget Danmark

Patent application No.: PA 1999 00991

Date of filing: 08 July 1999

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This is to certify the correctness of the following information:

The attached document is a true copy of the following document:

- The specification, claims, and abstract as filed with the application on the filing date indicated above.

Patent- og Varemærkestyrelsen
Kongeriget Danmark

Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

11 February 2003

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PATENT- G VAREMÆRKESTYRELSEN

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TREATMENT OF GENERAL ANXIETY DISORDER OR PANIC ATTACKS

H. Lundbeck A/S
Valby, Copenhagen

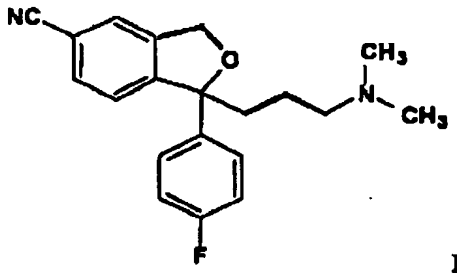
TREATMENT OF GENERAL ANXIETY DISORDER OR PANIC ATTACKS

Field of invention

The present invention relates to the use of the S-enantiomer of the well known antidepressant drug citalopram, i.e. (S)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile or a pharmaceutically acceptable salt thereof for the preparation of medicaments for the treatment of anxiety or panic attacks.

Background of the Invention

Citalopram is a well known antidepressant drug that has now been on the market for some years and has the following structure:



Formula I

It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, **1982**, *6*, 277-295 and A. Gravem, *Acta Psychiatr. Scand.*, **1987**, *75* , 478-486. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A 474580.

The (S)-enantiomer of citolopram ((+)-citalopram) and a method for its preparation is disclosed in US Patent No 4,943,590. The stereo selectivity of citalopram, i.e. the 5-HT-reuptake inhibition in the S-enantiomer, and accordingly the antidepressant effects of said enantiomer are also disclosed. S-citalopram is now in development as an antidepressant.

Studies have shown that patients suffering from generalised anxiety and panic attacks, in particular in association with agoraphobia, have a quality of life impairment comparable with or greater than the disability found in patients with alcoholism, schizophrenia or personality

disorders. Furthermore, current treatments are not always effective or cause unacceptable side-effects.

Consequently, there is a need for alternative therapies useful in the treatment of general anxiety disorder and disorders associated with panic attacks.

S-citalopram has now been found to show superior anxiolytic effect and improved effect in the treatment of panic attacks as compared to citalopram racemate

It has now, surprisingly, been found that the compound of the invention shows a beneficial effect in the treatment of panic attacks.

Description of the Invention

According to the present invention, a novel use of the (S)-enantiomer of citalopram, namely for the preparation of a medicament useful in the treatment of generalised anxiety disorder or panic attacks is provided.

The term generalised anxiety disorder (GAD) is as defined in DSM IV.

The phrase "treatment of panic attacks" contemplates treatment of any disease which is associated with panic attacks including panic disorder, specific phobias, social phobia and agoraphobia in which panic attacks occur. These disorders are further defined in the DSM IV. A panic attack is a discrete period in which there is a sudden onset of intense apprehension, fearfulness or terror, often associated with feelings of impending doom. During the attack symptoms such as palpitations, sweating, trembling, sensations of shortness of breath, feeling of choking, chest pain or discomfort, nausea, feeling dizzy, feelings of unreality, fear of losing control or going crazy, fear of dying, paresthesias and chills or hot flushes are present.

Panic disorders are characterised by recurrent unexpected panic attacks about which there is a persistent concern. Agoraphobia is anxiety about, or avoidance of, places or situations from which escape might be difficult or in which help may not be available in the event of a

panic attack. Specific phobia and social phobia (together formerly simple phobia) are characterised by marked and persistent fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation (flying, heights, animals, seeing blood etc.) or social performance situations.

The disorders in which panic attacks occur are differentiated from each other by the predictability of the occurrence of the attacks, for example, in panic disorder the attacks are unpredictable and not associated with any particular event, whereas in specific phobia the attacks are triggered by specific stimuli.

The phrase "treatment of panic disorder" means a reduction in the number or prevention of attacks and/or relief of the severity of the attacks. Similarly the term "treatment of generalised anxiety disorder" includes treatment or prevention of the disease, and relief of the symptoms thereof.

According to the invention the (S)-enantiomer of citalopram may be used as the base of the compound or as a pharmaceutically acceptable acid addition salt thereof or as an anhydrate or hydrate of such salt. The salts of the compound used in the invention are salts formed with non-toxic organic or inorganic acids.

The (S)-enantiomer of citalopram has been found to show effects different from and superior to those of the racemate in the "Inhibition of footshock-induced ultrasonic vocalisation in adult rats" - test, which is a standard animal model for anxiolytic effect or effect on panic attacks.

According to the invention, the (S)-enantiomer of citalopram or a pharmaceutically acceptable salt thereof may be administered in any suitable way e.g. orally or parenterally, and it may be presented in any suitable form for such administration, e.g. in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. Preferably, and in accordance with the purpose of the present invention, the compound of the invention is administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule or in the form of a suspension, solution or dispersion for injection.

Methods for the preparation of solid pharmaceutical preparations are well known in the art. Tablets may thus be prepared by mixing the active ingredients with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a convenient tabletting machine. Examples of adjuvants or diluents comprise: corn starch, lactose, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive such as colourings, aroma, preservatives, etc. may also be used provided that they are compatible with the active ingredients.

The compound of the invention is most conveniently administered orally in unit dosage forms such as tablets or capsules, containing the active ingredient in dosis of from about 0.1 mg to 100 mg, preferably 5 mg/day to 40 mg/day, preferably 10 mg/day to 20 mg/day, most preferably 0.1 mg/day to 1.0 mg/day.

The S-enantiomer of citalopram can be prepared as described US Patent No 4,943,590 and the base and other pharmaceutically acceptable salts may be obtained therefrom by standard procedures.

Thus the acid addition salts used according to the invention may be obtained by treatment of (S)-citalopram with the acid in an inert solvent followed by precipitation, isolation and optionally re-crystallisation by known methods and if desired micronisation of the crystalline product by wet or dry milling or another convenient process, or preparation of particles from a solvent-emulsification process.

Pharmacological Tests

The anxiolytic effect of (S)-citalopram and the citalopram racemate was tested in the footshock- induced vocalisation test in adult rats (described in detail in Sánchez C., Effect of serotonergic drugs on footshock-induced ultrasonic vocalization in adult male rats. Behav. Pharmacol. 1993; 4:267-277).

Experimental Procedure

Male rats (Wistar WU, Charles River, Germany), weighing 150-175 g at the beginning of the study were used.

Briefly, test cages (22 cm x 22 cm x 22 cm) made of grey Perspex and equipped with a metal grid floor were used. Footshocks were delivered from a two pole shocker and a microphone sensitive to ultrasounds in the range of 20-30 kHz was placed in the centre of the lid of the test cage. The ultrasounds were sent from the microphone to a preamplifier and converted from AC signals to DC signals in a signal rectifier. The accumulated time, in which the voltage of the rectified signal was larger than the voltage of a previously determined treshold level, was recorded.

Twenty-four hours before the first test session the animals were primed. A rat was placed in each test cage and received immediately thereafter four 1.0 mA inescapable footshocks each of a duration of 10 sec and with an intershock interval of 5 sec. The animals were left in the test cage for 6 min after the last shock. On test days drug or saline was given 30 min before test. The rats received four 1.0 mA inescapable footshocks each of a duration of 10 sec. The intershock interval was 5 sec. Recording of ultrasonic vocalisation started 1 min after the last shock and lasted for 5 min. The total time spent on vocalisation was recorded. After a wash-out period of one week the rats were used in a new test session. The rats were used for a total 7-8 weeks. At each test session the animal groups were randomly allocated to treatment with saline or test drug. Each treatment group consisted of 8 animals, one saline and 2-4 drug treated groups were included at each session. Each drug was tested at least in two separate experiments with overlapping doses.

Results

The experiments showed that the maximum effect was 60-70% inhibition for the racemate whereas the (S)-enantiomer was able to inhibit vocalisation completely.

This shows that the racemate has more "partial" effects in such studies whereas (S)-citalopram is a more full antagonist and accordingly the (S)-enantiomer has more potent and better anxiolytic effects and effects on panic attacks than the racemate.

Claims

1. Use of the (S)-enantiomer of citalopram or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment of generalised anxiety disorder or panic attacks.

2. The use according to Claim 1, **characterised in**, that the medicament is for administration as a unit dose.

3. The use according to Claim 1 or 2, **characterised in**, that the unit dose is containing the active ingredient in an amount from 0.1 mg to 100 mg, preferably 5 mg/day to 40 mg/day, preferably 10 mg/day to 20 mg/day, most preferably 0.1 mg/day to 1.0 mg/day.

4. Use of any of Claims 1 to 3, **characterised in**, that the medicament is for the treatment of generalised anxiety disorder

5. Use of any of Claims 1 to 3, **characterised in**, that the medicament is for the treatment of panic attacks.

6. Use of any of Claim 5, **characterised in**, that the medicament is for the treatment of panic disorder.

7. Use of any of Claim 5, **characterised in**, that the medicament is for the treatment of specific phobias.

8. Use of any of Claim 5, **characterised in**, that the medicament is for the treatment of social phobia.

9. Use of any of Claim 5, **characterised in**, that the medicament is for the treatment of agoraphobia.

Abstract

Use of the (S)-enantiomer of citalopram or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment of generalised anxiety disorder or panic attacks.